REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-2, 4-10, 13-18, 21-35 and 42-47 are pending. Claims 1 and 13 have been amended. Claims 2, 11-12, 19-20 and 36-41 have been cancelled without prejudice or admission.

Claim 1 has been amended without prejudice to delete the term "about" and to amend the dosage range to recite "200 to 1200 micrograms". Support for this amendment can be found, for example, in the original claims.

Reconsideration is respectfully requested.

II. Double Patenting

In the Office Action, claims 1-2, 10, 12-18 and 22-26 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 11, 16 and 30-33 of copending U.S. Application No. 10/621,964.

In response, Applicants respectfully submit that the filing of a terminal disclaimer will be considered upon notification that the pending claims are otherwise allowable.

III. Claim Rejections- 35 U.S.C. § 103

A. Gupta et al. in view of Lucas et al.:

In the Office Action, claims 1-2, 4-10, 12-18, 21-28 and 42 were rejected under 35 U.S.C. § 103(a) as being anticipated by Gupta et al. (U.S. 2002/0006933 in view of Lucas et al. (Pharmaceutical Research 1999, Vol. 16, No. 10, pgs. 1643-1647).

Independent claim 1 as amended recites:

> "A composition for treating sexual dysfunction by pulmonary inhalation, said composition comprising apomorphine, the apomorphine being in the form of a free base, pharmaceutically acceptable salt or ester, wherein the composition provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt); wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration; wherein the composition is a dry powder composition; and wherein the apomorphine has a mass median aerodynamic diameter of 10 μm or less."

The claims of the present invention are directed to a composition for treating sexual dysfunction by pulmonary inhalation of a dry powder composition comprising a low dose of apomorphine (***200-1200 μg***), wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration.

In the Office Action, the Examiner indicated that that Gupta reference teaches 'an equivalent dose 3-12 mg in humans or a 3000-12,000 micrograms human dose [and] further contends that in light of applicant's recitation of the term "about" such dosage of 3000 micrograms does indeed render obvious applicant's recitation of about 1600 micrograms of apomorphine' because adjusting the concentration of apomorphine would be within the purview of the skilled artisan. (OA, page 12, 3rd paragraph).

In response, the Examiner's attention is directed to amended independent claim 1, wherein the term "about" has been deleted from the claim. Furthermore, the claimed dosage range has been amended to recite 200 to 1200 micrograms. Accordingly, the dosage range claimed in amended independent claim 1 of the present invention does not overlap with the dosage range described in the Gupta reference.

Also in the Office Action, the Examiner cited pages 7, paragraph 0072 of the Gupta reference for teaching that Cmax was achieved immediately. (Office Action, page 13, 1st paragraph). Applicant's respectfully submit that there is no basis within the Gupta reference for this assertion. In fact, the lowest Tmax described in the Gupta reference using any delivery route

is 0.17 hrs (10.2 minutes). The Examiner refers to Page 7, Para 72 for supporting the statement that Cmax is achieved immediately following administration. The only reference to the word "immediately" in this paragraph is to state that **plasma samples were obtained immediately**. Peak plasma levels from the doses mentioned in this paragraph are shown in Table 7 and these were only obtained in all cases in over 30 minutes. Accordingly, Applicant maintains that Gupta does not provide any indication of Cmax being achieved in less than 10.2 minutes. Moreover, Gupta does not discuss the desirability of achieving Cmax quickly.

In the Office Action, the Examiner further indicated that "while the exact dosages of the ingredients are not disclosed by Gupta, et al. it is generally noted that differences in concentration do not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or dosage is critical." (Office Action, page 14, 2nd paragraph). The Examiner relies on *In re Aller* to allege that the claimed dosage range represents an optimization through routine experimentation and that this is obvious in the absence of indications that the claimed dosage range is critical.

In response, Applicants respectfully submit that the presently claimed invention achieves unexpected results. A primae facie case of obviousness of based on "overlapping" ranges can be rebutted upon a showing of the criticality of the claimed range. (See: MPEP Sec. 2144.05, III, citing *In re Woodruff*, "The law is replete with cases in which the differences between the claimed invention and the prior art is some range or other variable within the claims…In such a situation, the applicant must show that a particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range."). One of the contributions made by the presently claimed invention is the provision of Cmax within 1 to 5 minutes of administration while also avoiding side effects by means of the composition claimed in claim 1. This ability of a low dosage (e.g., 200-1200 micrograms) to achieve this effect is **unpredictable and unexpected**. The prior art, specifically Gupta *et al*, does not provide any indication that the claimed dosage of apomorphine would be suitable for treating sexual dysfunction in humans and that Cmax will be achieved within 1 to 5 minutes. In fact, looking at the teaching of Gupta, the skilled person would understand that a dosage of 3 -12 mg was taught

for achieving the required therapeutic effect and that this effect was achieved in over 10 minutes by inhalation irrespective of the dosage. Therefore, the claimed dosage is significantly lower than the lowest end of the range described in the Gupta reference. There is no other prior art cited by the Examiner which suggests the claimed dosage. Therefore, the skilled person will have no reason and will, in fact, be dissuaded from reducing the dosage.

Furthermore, the prior art provides no indication that the dosage of apomorphine in a composition as claimed in claim 1 has any effect on the result of achieving quicker Tmax. Indeed, quite the opposite. The Tmax in Gupta is completely independent of concentration – see table 4. Gupta does not recognize that Tmax (known effect) can be attributed to the dosage or any of the other characteristics mentioned in claim 1 (claimed parameter). Therefore, the requirement of result – effective variable is not met and this objection does not apply.

Moreover, the dosage specified in the claim is critical in view of the stated aim to provide enough apomorphine to provide a therapeutic effect in a quick time while reducing side effects. The dosage in combination with the other specific characteristics of the composition specified in claim 1 achieves this objective. The skilled person would have no motivation to reduce the dosage in view of the teaching of the prior art because Gupta teaches the equivalent range of 3000 - 12000 micrograms in humans, much higher that claimed, and teaches that side effects were less of a concern in humans (Page 5, lines 1 to 3 of Gupta). Example 15 (page 60, lines 13 of the PCT publication) clearly shows that the higher values in the dosage range specified in amended claim 1 was not associated with any serious side effects which are observed with apomorphine.

Achieving a quicker Tmax and onset of therapeutic effect on providing a lower dose of apomorphine is something that cannot be predicted from the Gupta reference. Gupta in table 4 only shows a Tmax at 10. 2 minutes (.17 hr) irrespective of the dosage used. Even when the dosage is reduced in Gupta from 2 mg to 0.5 mg in table 4 the Tmax remains constant. Hence, there is no suggestion in Gupta that dry powder inhalation of lower doses could achieve a much quicker Tmax. Therefore, the fact that Tmax can be achieved in about half the time as in the

inhalation example in Table 4 of Gupta by providing almost half or less of the human dosage specified in Gupta is an unexpected result which cannot be predicted or arrived at by the ordinary skilled person without any inventive faculties.

In addition to the data in the application (e.g., Example 15) which supports that the claimed composition and dosage range is effective in achieving the Cmax within 1 to 5 minutes and, at the very least, the finding of reduced Tmax with lower dosage is unexpected and could not have been predicted by the skilled person, Applicants further submit herewith a press release (Annex 1) showing the effects of some further doses within the claimed range and a slide from a clinical study mentioned in the press release showing the difference between onset of therapeutic effects and Tmax (Annex 2) to support our arguments. The study referred to in this press release was a double-blind, placebo-controlled trial designed to assess the safety and efficacy of apomorphine for the treatment of sexual dysfunction. The study evaluated three fine particle doses (100 µg, 150 µg and 200 µg). Please note that the fine particle doses of 100 µg, 150 µg and 200 µg correspond to Nominal Doses (i.e. doses contained within the blister) of 220 µg, 310 µg and 430 µg respectively. The results show that the lowest dose (220 µg nominal dose), is effective. The additional data presented in the press release clearly demonstrates that a statistically significant effect for the above-mentioned doses was measured in a subsequent clinical study. Annex 1 also states that 60% of patients responded with 5 minutes of dosing and 85 % of patients responded with 10 minutes of dosing. The Examiner's attention is also directed to the fact that the response time refers to the onset of therapeutic effect which is different to Tmax (time taken to achieve Cmax). Annex 2 clarifies the relationship between Tmax and onset of effect for the clinical study. As can be seen, the Tmax for the doses in Annex A for 85% of the patients in the study would be within the claimed range.

Lucas et al., (Pharmaceutical Research, 1999; 16(10):1643-1647) does not cure aforementioned defects of the Gupta publication. Specifically, Lucas et al. fails to teach a composition that "provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt)" as recited in amended claim 1 of the present invention. In fact, while Lucas

et al. is concerned with inhalation therapy, and is cited for describing similar particle size ranges or excipients/propellants used for an inhalation composition, Lucas et al. does not relate to apomorphine or treatments for sexual dysfunction and thus cannot be readily adapted to, or readily applied to modify, the teaching of the Gupta publication in order to cure the defects of the primary reference.

Lucas et al. does not describe a composition "wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration" as recited in amended claim 1 of the present invention. A person skilled in the art concerned with the administration of apomorphine for the treatment of sexual dysfunction would therefore not find in the Lucas reference any teaching or suggestion regarding the relatively low dose and relatively rapid onset of therapeutic effect provided by the subject invention, which are claimed in the subject application, but are clearly missing from the Gupta publication.

Therefore, inhalation of a "composition comprising apomorphine, the apomorphine being in the form of a free base, pharmaceutically acceptable salt or ester, wherein the composition provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt); wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration" as recited in amended claim 1 of the present invention would not have been obvious from the Gupta publication, taken alone, or in combination with the Lucas et al. reference.

B. Gupta et al. in view of Vervaet et al.:

In the current Office Action, claims 29-35 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gupta et al. (U.S. Publication No. 2002/0006933) as applied to Claims 1 to 2, 4-10, 12-18, 21-28, and 42 above and in further view of Vervaet et al. (International Journal of Pharmaceutics, 1999, Vol. 186, pgs. 13-30).

Applicants reiterate the arguments presented above with regard to the Gupta reference.

The Vervaet et al. describes "an overview of the present state of the art with respect to the formulation of MDIs." See Vervaet, abstract.

Vervaet et al. (International Journal of Pharmaceutics, 1999, Vol. 186, pgs. 13-30) does not cure aforementioned defects of the Gupta publication. Specifically, Vervaet et al. fails to teach a composition that "provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt)" as recited in amended claim 1 of the present invention. Vervaet et al. does not relate to apomorphine or treatments for sexual dysfunction and thus cannot be readily adapted to, or readily applied to modify, the teaching of the Gupta publication in order to cure the defects of the primary reference.

Vervaet et al. does not describe a composition "wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration" as recited in amended claim 1 of the present invention. A person skilled in the art concerned with the administration of apomorphine for the treatment of sexual dysfunction would therefore not find in the Vervaet et al. reference any teaching or suggestion regarding the relatively low dose and relatively rapid onset of therapeutic effect provided by the subject invention, which are claimed in the subject application, but are clearly missing from the Gupta publication.

Therefore, inhalation of a "composition comprising apomorphine, the apomorphine being in the form of a free base, pharmaceutically acceptable salt or ester, wherein the composition provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt); wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration" as recited in amended claim 1 of the present invention would not have been obvious from the Gupta publication, taken alone, or in combination with the Vervaet et al. reference.

As discussed above, the present Response refers primarily to independent claim 1 of the present invention, however, the patentability of the dependent claims 29 to 35 follow at least for the reason of being dependent from the independent claim 1 that is patentable.

In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) to claims 29 to 35 as being unpatentable over Gupta et al. (U.S. 2002/0006933) in view of Vervaet et al. (International Journal of Pharmaceutics, 1999, Vol. 186, pgs. 13-30) is respectfully requested.

C. Gupta et al. in view of Pierre et al.:

In the current Office Action, claims 43-44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gupta et al. (U.S. Publication No. 2002/0006933) as applied to Claims 1-2, 4-10, 12-18, 21-28 and 42 above and in further view of Pierre et al. (Annals of Allergy, Asthma and Immunology, April 1999, Vol. 82, No. 4, pgs. 377-382, abstract).

Applicants reiterate the arguments presented above with regard to the Gupta reference.

Pierre et al. describes a study which "compares the efficacy and safety of one and two actuations of albuterol sulfate powder delivered via a breath-actuated, effort-assisted, investigational inhaler (Spiros, Dura Pharmaceuticals, Inc) and albuterol delivered via a conventional propellant-driven metered dose inhaler (Ventolin, Glaxo, Inc)." See Pierre et al., abstract.

Pierre et al. does not cure aforementioned defects of the Gupta publication. Specifically, Pierre et al. fails to teach a composition that "provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt)" as recited in amended claim 1 of the present invention. Pierre et al. does not relate to apomorphine or treatments for sexual dysfunction and thus cannot be readily adapted to, or readily applied to modify, the teaching of the Gupta publication in order to cure the defects of the primary reference.

Pierre et al. does not describe an apomorphine composition "wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration" as recited in amended claim 1 of the present invention. A person skilled in the art concerned with the administration of apomorphine for the treatment of sexual dysfunction would therefore not find in the Pierre et al. reference any teaching or suggestion regarding the relatively low dose and relatively rapid onset of therapeutic effect provided by the subject invention, which are claimed in the subject application, but are clearly missing from the Gupta publication.

Therefore, inhalation of a "composition comprising apomorphine, the apomorphine being in the form of a free base, pharmaceutically acceptable salt or ester, wherein the composition provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt); wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration" as recited in amended claim 1 of the present invention would not have been obvious from the Gupta publication, taken alone, or in combination with the Pierre et al. reference.

As discussed above, the present Response refers primarily to independent claim 1 of the present invention, however, the patentability of the dependent claims 43 and 44 follow at least for the reason of being dependent from the independent claim 1 that is patentable.

In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) to claims 43 and 44 as being unpatentable over Gupta et al. (U.S. 2002/0006933) in view of Pierre et al. (Annals of Allergy, Asthma and Immunology, April 1999, Vol. 82, No. 4, pgs. 377-382, abstract) is respectfully requested.

D. Gupta et al. in view of Snow et al.:

In the current Office Action, claims 45-47 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gupta et al. (U.S. Publication No. 2002/0006933) as applied to Claims 1-2, 4-

10, 12-18, 21-28, and 42 above and in further view of Snow (U.S. Publication No. 2002/0134382).

Applicants reiterate the arguments presented above with regard to the Gupta reference.

Snow (U.S. Publication No. 2002/0134382) describes "a medicament container configured to improve entrainment of the medicament in the air and to improve deposition of the medicament in the lungs includes an upper layer and a bottom layer with medicament disposed therebetween." See Snow, abstract.

The Snow publication does not cure aforementioned defects of the Gupta publication. Specifically, the Snow publication fails to teach a composition that "provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt)" as recited in amended claim 1 of the present invention. The Snow publication does not relate to apomorphine or treatments for sexual dysfunction and thus cannot be readily adapted to, or readily applied to modify, the teaching of the Gupta publication in order to cure the defects of the primary reference.

The Snow publication does not describe an apomorphine composition "wherein the administration of the composition by pulmonary inhalation provides a Cmax within 1 to 5 minutes of administration" as recited in amended claim 1 of the present invention. A person skilled in the art concerned with the administration of apomorphine for the treatment of sexual dysfunction would therefore not find in the Snow publication any teaching or suggestion regarding the relatively low dose and relatively rapid onset of therapeutic effect provided by the subject invention, which are claimed in the subject application, but are clearly missing from the Gupta publication.

Therefore, inhalation of a "composition comprising apomorphine, the apomorphine being in the form of a free base, pharmaceutically acceptable salt or ester, wherein the composition provides a nominal dose of apomorphine of from 200 to 1200 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof (based on the weight of the hydrochloride salt); wherein the administration of the composition by pulmonary inhalation provides a Cmax within

1 to 5 minutes of administration" as recited in amended claim 1 of the present invention would not have been obvious from the Gupta publication, taken alone, or in combination with the Snow publication.

As discussed above, the present Response refers primarily to independent claim 1 of the present invention, however, the patentability of the dependent claims 45 to 47 follow at least for the reason of being indirectly dependent from the independent claim 1 that is patentable.

In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) to claims 45 to 47 as being unpatentable over Gupta et al. (U.S. 2002/0006933) in view of Snow (U.S. Publication No. 2002/0134382) is respectfully requested.

CONCLUSION

The Commissioner for Patents is hereby authorized to charge the fees due for submission of the Request for Continued Examination ($810.00) and for the petition for two-month extension of time ($490.00) due under 37 C.F.R. 1.17(e) and 1.17(a)(2). It is believed that no additional fees are due for this submission. If it is determined that any additional fees are due or that any fee has been overpaid, the Commissioner for Patents is hereby authorized to charge said fees or credit any overpayment to Deposit Account No. 50-0552.

Reconsideration of the present application, as amended, is requested. The Examiner is respectfully requested to telephone Applicant's undersigned attorney in order to resolve any outstanding issues and advance the prosecution of the case to allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
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